IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant: Kai-Uwe Lewandrowski and Debra J. Trantolo

Serial No.: 10/054,171 Art Unit: 1617

Filed: January 17, 2002 Examiner: Gina C. Yu

For: *METHODS OF DIAGNOSIS AND TREATMENT OF OSTEOPOROSIS*

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-19 in the Office Action mailed July 1, 2004, in the above-identified patent application. A Notice of Appeal was filed on November 1, 2004. The Commissioner is hereby authorized to charge $500.00, the fee for the filing of this Appeal Brief for a large entity, to Deposit Account No. 50-3129.

This Appeal Brief is accompanied by a Petition for Revival of an Application for Patent Abandoned Unintentionally Under 37 CFR 1.137(b) and the authorization to charge $1,500.00, the fee for filing this Petition for a large entity, to Deposit Account No. 50-3129. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is DePuy Mitek, Inc., a subsidiary of Johnson & Johnson, that recently acquired this technology from Cambridge Scientific, Inc., Cambridge, MA, the assignee.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS

Claims 1-19 are pending. Claims 20-29 have been cancelled. Claims 1-19 are on appeal. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

An amendment after final rejection was filed via facsimile transmission on October 1, 2004. In the Advisory Action mailed November 26, 2004, the Examiner indicated that this amendment would not be entered. The claims were last amended in the Amendment and Response filed on November 26, 2003. An appendix sets forth the claims on appeal.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 defines a method of detecting osteoporosis in a individual to be tested comprising (see at least page 3, lines 26-27 and page 26, line 26 to page 27, line 2): a) obtaining a sample of a bone related tissue or cells (see at least page 3, lines 27-28); b) assaying the concentration of at least one marker selected from the group consisting of infectious agents, a

factor produced by an infectious agent, and heat shock proteins (HSPs) produced in response to an infectious agent (see at least page 3, line 28 to page 4, line 1, page 4, lines 23-25, page 4, line 29 to page 5, line 2, page 5, lines 25-29 and page 24, lines 17-20), and c) comparing the concentration of the at least one marker with the concentration of the marker in a sample of the same bone related tissue or cells from a control individual who does not have osteoporosis (see at least page 4, lines 1-4).

Dependent claim 2 defines the method of claim 1 further comprising comparing the concentration of a first marker with concentrations of same marker obtained from the same individual over a period of time (see at least page 4, lines 1-4).

Dependent claim 3 defines the method of claim 1 wherein the marker is a heat shock protein ("HSP") and the bone related tissue or cells are obtained under conditions that do not induce a change in the amount of one or more HSPs in the tissue or cells (see at least page 19, lines 10-12).

Dependent claims 4, 7, 8 and 9 define methods wherein the HSP is HSP 70, HSP 60, HSP 90, gp 96, cpn10, cpn20, ubiquitin, or cpn 30 (see at least page 4, lines 4-6).

Dependent claim 5 defines the method of claim 2 wherein the time period between the first assay and the second assay is at least about 12 hours (see at least page 4, lines 14-16).

Dependent claim 6 defines the method of claim 1 wherein the sample comprises bone cells or body fluid (see at least page 3, lines 27-28).

Dependent claims 10 and 11 define methods wherein the concentration of HSP is measured using an immunoassay or using an assay for a nucleotide molecule encoding HSP, respectively (see at least page 4, lines 16-19).

Dependent claims 12 and 13 define methods wherein the infectious agent is selected from the group consisting of bacteria, viruses, protozoa, parasites and fungi or selected from the group consisting of bacterial produced factors, viral produced factors, protozoal produced factors, parasitic produced factors and fungal produced factors, respectively (see at least page 4, lines 23-25 and page 4, line 29 to page 5, line 2).

Dependent claims 14 and 19 define methods wherein the bacteria is selected from the group consisting of *Staphylococcus aureus*, *Porphyromonas gingivallis*, *Eikenella corrodens*, *Actinobacilus actinomycetemcomitans*, *Prevotella intermedia*, *Campylobacter* rectus, *Staphylococcus epidermidis*, *Salmonella spp.*, *Escherichia coli*, *Neisseria gonorrhoea*, *Neisseria meningitis*, *Mycobacterial tuberculosis*, *Haemophius influenzae*, *Pasteurella multocida*, *B. bronchiseptica*, and *Fusobacterium nucleatum* or selected from the group consisting of *Staphylococus aureus*, *Actinobacillus actinomycetemcomitans* , *Bordetella bronchiseptica*, and *Fusobacerium nucleatum*, respectively (see at least page 4, lines 6-13).

Dependent claims 15, 16, 17 and 18 define methods wherein the infectious agent is a bacterially produced factor selected from the group consisting of endotoxin-LPS, gapstatin, and dermonecrotic toxin (DNT), or selected from the group consisting of gapstatin and dermonecrotic toxin, or wherein the factor is gapstatin, or wherein the factor is dermonecrotic toxin, respectively (see at least page 4, lines 13-14).

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues presented on appeal are:

(1) whether claims 1-19 are enabled as required by 35 U.S.C. § 112, first paragraph;

(2) whether claims 1-6, 8 and 11 are non-obvious under 35 U.S.C. § 103(a) over International Publication No. WO 00/13024 to Findlay ("Findlay") in view of Nair, et al., "Molecular Chaperones Stimulate Bone Resorption" *Calcified Tissue International* 64:214-218 (1999) ("Nair"); and

(3) whether claims 1, 12-14 and 19 are non-obvious under 35 U.S.C. § 103(a) over Findlay in view of Reddi, et al., "The *Escherichia coli* Chaperonin 60 (groEL) is a Potent Stimulator of Osteoclast Formation" *Journal of Bone and Mineral Research* 13(8):1260-1266 (1998) ("Reddi").

(7) GROUPING OF CLAIMS

The claims do not stand or fall together. Reasons for this grouping and arguments for the separate patentability of these groups of claims are provided below.

(8) ARGUMENT

(i) Rejection under 35 U.S.C. § 112, first paragraph, enablement

Claims 1-19 have been rejected as not enabled as required by 35 U.S.C. § 112, first paragraph, on the basis that "while being enabling for detection of osteoporosis caused by bacterial infection, does not reasonably provide enablement for detecting osteoporosis by measuring concentrations of other types of pathogens such as viruses, viral produced factors, protozoa,.....".

It is quite clear from the examiner's rejection of all claims that she has improperly failed to examine each claim separately in making this rejection, rather than examining the claims independently. Claims 12 and 19 are restricted to specific bacterial species as the etiological agents; claims 15-18 are restricted to specific bacterially produced factors.

Accordingly, claims 12, 15-18, and 19 should not have been included in the rejection since they are limited to bacteria.

Claims 1-11, 13, and 14, which relate more generally to detection of a marker associated with an infectious agent, factor produced by an infectious agent, or heat shock protein (which is endogenous to cells and tissue, but whose expression is altered upon infection with an infectious agent) as a means of detecting osteoporosis, are enabled, as discussed below

The Legal Standard for Enablement

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See, e.g., *Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 (Fed. Cir. 2003) and *Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); and *In re Stephens*, 529 F.2d 1343 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). In addition, as

affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir.1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation ' must not be unduly extensive.' *In re Atlas Powder Co., v. E.I. DuPont De Nemours & Co.* , 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984).

As noted in *Ex parte Jackson*, the test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. See *Ex parte Jackson*, 217 USPQ 804, 807 (PTO Bd. App. 1982). The adequacy of a specification's description is not necessarily defeated by the need for

some experimentation to determine the properties of a claimed product. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F3d 956, 965-966 63 USPQ2d 1609, 1614 (Fed. Cir. 2002). There is no requirement for examples.

As the Board of Patent Appeals recently quoted in another case,

"Nevertheless, "[w]hen rejecting a claim under the enablement requirement of section 112," it is well settled that "the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." As discussed below, the Examiner has not met the initial burden of setting forth a reasonable explanation as to why the claims of the present application are not enabled.

Analysis

Osteoporosis is a systemic disorder characterized by decreased bone mass and microarchitectural deterioration of bone tissue leading to bone fragility. Current techniques for detecting osteoporosis are using biochemical markers, radiography and measurement of bone mineral density (BMD). However, these techniques are limited by cost or accuracy.

Appellants have discovered that osteoporosis can be caused by infectious agents such as viruses, bacteria, fungi, protozoa or parasites (see at least page 4, lines 23-25) and that one can screen rather inexpensively for osteoporosis by assaying the concentration of at least one marker

selected from the group consisting of infectious agents, factors produced by infectious agents, and heat shock proteins produced in response to an infectious agent.

The basis for the rejection for lack of enablement is not that the Examiner does not believe one can make and use the claimed method, but that the examiner does not believe the method works for anything other than bacterial infection.

The examiner has provided nothing in support of this rejection other than her assertions and by reference to Nair on the basis that Nair states that not all bacterial molecular chaperones stimulate bone resorption. Appellants are puzzled as to why this has anything to do with the method of detecting osteoporosis as defined by the claims. The claims do not define a method for detecting the cause of osteoporosis, the claims define a method for detecting osteoporosis by assaying for the presence of an infectious agent or a factor produced by an infectious agent or heat shock proteins produced in response to an infectious agent, any one of which can cause the osteoporosis.

Moreover, the examiner has agreed that the claims are enabled for detecting osteoporosis where bacteria are involved. Nair provides no evidence that one skilled in the art would not extrapolate from bacteria to viruses or protozoa.

In contrast, Appellants have described the known association of certain parasites and protozoans with bone disease (See page 34) and the association of a number of viruses with production of HSPs (pages 39-40; 31-32).

While Appellants maintain that the Examiner has not met the initial burden of setting forth a reasonable explanation as to why the claims of the present application are not enabled, an

analysis of the Wands factors clearly demonstrates that claims 1-19 are enabled by the specification of the present application.

Claim 1 defines a method of detecting osteoporosis in a individual to be tested by (1) obtaining a sample of bone-related tissue or cells, (2) assaying the concentration of a marker selected from the group of infectious agents, factors produced by infectious agents, and heat shock proteins produced in response to an infectious agent, and (3) comparing the concentration of the at least one marker with the concentration of the marker in a sample of the same bone related tissue or cells from a control individual who does not have osteoporosis.

Methods of obtaining a sample of bone related tissue or cells from an individual are well known in the art. Methods of assaying the concentration of a marker are also well known in the art and are disclosed in the specification at least at page 8, lines 4-29, and at page 9, lines 1-12. Methods of comparing the concentration of a marker from an individual with the concentration of said marker from a control individual are well known in the art and are disclosed in the specification at least at page 11, lines 21-28, and at page 19, lines 19-21. Furthermore, the examiner admits in the office action mailed July 1, 2004 at page 3 lines, 15-17 and in the advisory action on page 2, that general methods for obtaining a sample of bone related tissue or cells from an individual; of assaying the concentration of infectious agents or factors produced by infectious agents or heat shock proteins produced in response to infectious agents; and of comparing the concentration of a marker from an individual to a control individual are well known in the art. This is all that is required to practice the method of detecting osteoporosis as

defined by the claims of the present application. While measurement of these factors may require experimentation, one of skill in the art typically engages in such experimentation.

It is clear from the discussion above that the quantity of experimentation to perform the method as defined by the claims is minimal, that the skill of one in the art is high and that the specification provides sufficient guidance for one of skill in the art to perform the method as defined by the claims. It would not require undue experimentation to perform the method for detecting osteoporosis as defined by the claims 1-19. Therefore, claims 1-19 are enabled by the specification.

(ii) Rejections Under 35 U.S.C. § 103

Claims 1-6, 8 and 11 were rejected under 35 U.S.C. § 103 as obvious over Findlay in combination with Nair. Claims 1, 12-14, and 19 were rejected under 35 U.S.C. § 103 as obvious over Findlay in combination with Reddi.

Claim 7, 9, 10, and 15-18 have not been rejected over the prior art. These claims differ from the rejected claims based on being specific to HSP60 (claim 7), ubiquitin (claim 9), where the concentration of the agent to be detected is measured using an immunoassay (claim 10), wherein the agent to be detected is a bacterially produced factor: endotoxin-LPS, gapsttin, and dermonectrotic toxin (claims 15-18).

The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on appellant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The references cited by the Examiner do not meet all three criteria.

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier* , 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

The Court of Appeals for the Federal Circuit warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the describing or motivation to combine prior art references."

In re Dembiczak, 175 F.3d 994 at 999 (Fed. Cir. 1999). The Examiner has not provided such a showing.

Analysis

1. Rejection of claims 1-6, 8 and 11 over Findlay in view of Nair

Findlay

Findlay discloses a method of measuring **internal** regulators of bone remodeling as a predictive measure for the **potential** onset of certain skeletal disorders. Findlay discloses a method that includes the steps of taking a sample of body tissue or body fluid and measuring or estimating the level of a regulator of bone remodeling. Findlay discloses internal regulators of bone growth such as growth factors, cytokines, and associated proteins.

Findlay does not recognize a critical element of the claimed method: the discovery of an association between the development of osteoporosis and infectious agents.

Nair

Nair does not make up for the deficiency of Findlay. Nair measures the activity of molecular chaperones in a murine calvarial bone resorption assay. Nair recognizes that certain bacterial and mammalian molecular chaperones can stimulate bone resorption. Nair does not make the connection however, that one could screen for osteoporosis by detecting infectious agents, factors produced by infectious agents, or HSPs in one individual and comparing it with the levels in another.

The combination of Findlay and Nair

No where is there any suggestion in either reference of a screen for osteoporosis bases on an ***external stimulus for the disease.*** Findlay is looking at endogenous causes of osteoporosis. Nair is not looking at osteoporosis. Nowhere is there any teaching that would motivate one of skill in the art to move from Findlay, which teaches away from an external cause of osteoporosis, to Nair, which relates to a bone resorption assay, not osteoporosis, and arrive at the claimed method, much less with any reasonable expectation of success.

Findlay and Nair do not disclose each and every element of the claims as defined in the present application. Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). Findlay and Nair do not disclose or suggest a method of detecting osteoporosis in an individual that contains the steps of measuring an infectious agent such as bacteria, or a factor produced by an infectious agent, or **endogenous** factors that are altered in expression **due to infection**. Findlay and Nair certainly do not disclose or suggest measuring endogenous factors, such as heat shock proteins, that are **induced by infection** to detect osteoporosis in an individual. The Examiner has not pointed to a single place in Findlay or Nair that provides support for each of the elements of the claims as defined by the present application. The Examiner simply argues that the claims are obvious because Findlay describes an assay that measures **internal** regulators of bone remodeling and Nair states that molecular chaperonins can stimulate bone resorption. It

is clear that Findlay and Nair do not disclose each and every element of claims 1-19 of the present application.

In addition to disclosing each of the claimed elements, there must be some suggestion to modify or combine the reference teachings. One or ordinary skill in the art would not combine Findlay with Nair because neither reference provides the modifications that would bring the references into conformity with the claims of the present application. Furthermore, Findlay and Nair do not provide any motivation for one of skill in the art to combine these references. The Examiner has failed to identify a single place in Findlay or Nair that provides one of skill in the art with the motivation to combine these references.

Finally, Findlay and Nair do not provide one of ordinary skill in the art with a reasonable expectation of success. Findlay and Nair do not disclose, suggest or provide one of ordinary skill in the art with a reasonable expectation of success that assaying the concentration of an infectious agents, or a factor produced by an infectious agent, or **endogenous** factors that are altered in expression **due to an infectious agent** in bone related tissue or cells can be used to detect osteoporosis. Again, the Examiner has not provided any evidence of a reasonable expectation of success.

It is clear that to establish a *prima facie* case of obviousness the cited references must (1) recite each and every element of the claims, (2) provide one of skill in the art with the motivation to combine the cited references and (3) provide one of ordinary skill in the art with a reasonable expectation of success. The Examiner has not established a *prima facie* case of obviousness because the Examiner has not provided a reasonable expectation of success and has not provided

the motivation to combine the cited references. While the Examiner argues that Findlay and Nair disclose each and every element of the claims of the present application, it is clear from the discussion above that they do not. Even considering that the Examiner has established a *prima facie* case of obviousness, the claims are still not obvious because Findlay and Nair do not disclose each and every element of the claims, do not provide a motivation to combine and do not provide a reasonable expectation of success. Therefore, claims 1-6, 8 and 11 are not obvious over Findlay in view of Nair.

2. Rejection of claims 1, 12-14 and 19 over Findlay in view of Reddi

Findlay

As discussed above, Findlay discloses a method for a predictive assay that measures **internal** regulators of bone remodeling such as growth factors and cytokines as a predictive measure for the **potential** onset of certain skeletal disorders.

Reddi

Reddi states that cpn60 (groEL) from *E. coli* stimulates bone resorption and osteoclast formation in culture. Reddi also states that a protein on the surface of *Actinobacilus actinomycetemcomitans*, which causes periodontal disease, can stimulate bone resorption.

Reddi does not relate to osteoporosis. At most, Reddi shows that direct application of a HSP from a bacteria to the surface of bone allegedly can cause osteoclast mediated pit formation in the surface of the bone. Osteoporosis is not caused by direct application of a factor to bone cells, however, but is a decrease in bone density within the bone. One skilled in the art would not be able to extrapolate from studies relating to periodontal disease, which is totally different

from osteoporosis, to osteoporosis. Even Reddi acknowledges that his studies are distinct from studies involving osteoporosis, noting in the abstract "Whether endogenous ("self") chaperonins have a role in other bone loss disordes, such as osteoporosis, is an intringuing possibility". The authors certainly do not indicate that they would consider the results predictive of any other bone disorder; therefore neither should the examiner.

The combination of Findlay and Reddi

As discussed above, Findlay does not lead one of skill in the art to a method for detecting osteoporosis since Findlay does not recognize that infectious agents, directly or indirectly, can lead to osteoporosis. Findlay relates solely to endogenous (i.e., mammalian) HSPs. Reddi does not make up for this deficiency. Reddi relates to periodontal disease and looks at in surface pit formation mediated by osteoclasts; not alteration in bone density.

Findlay and Reddi do not disclose or suggest a method of detecting osteoporosis in an individual that contains the steps of measuring an infectious agent such as bacteria, or a factor produced by an infectious agent, or endogenous factors that are altered in expression due to infection. Reddi certainly does not disclose or suggest assaying endogenous heat shock proteins that are altered in expression due to an infectious agent. There is no teaching that would lead one of skill in the art to modify Findlay to measure infectious agents, or products thereof, instead of endogenous HSPs, with a reasonable expectation of success. Reddi does not even mention mammalian heat shock proteins in connection with bone resorption. It is clear that Findlay and Reddi do not disclose each and every element of the claims of the present application. Furthermore, Findlay and Reddi do not provide any motivation for one of skill in the art to

combine these references. One of ordinary skill in the art would not be motivated to combine Findlay and Reddi because they do not disclose each and every element of the claims.

The Examiner has again failed to establish a *prima facie* case of obviousness. The examiner has not identified a single place in Findlay or Reddi that provides one of skill in the art with the motivation to combine these references as appellants have done. Findlay and Nair do not disclose, suggest or provide one of ordinary skill in the art with a reasonable expectation of success that assaying the concentration of an infectious agents, or a factor produced by an infectious agent, or **endogenous** factors that are altered in expression **due to an infectious agent** in bone related tissue or cells can be used to detect osteoporosis.

Therefore, claims 1, 12-14 and 19 are not obvious over Findlay in view of Reddi.

(9) SUMMARY AND CONCLUSION

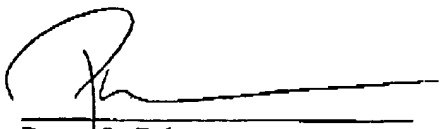
The Examiner has not met the initial burden of setting forth a reasonable explanation as to why the claims of the present application are not enabled. As admitted by the Examiner, claims based on measurement of bacteria, bacterial induced proteins, and HSPs are enablement. The examiner has not provided any reason one skilled in the art would not also have a reasonable expectation of success based on other etiological agents such as parasites or protozoa based on the data provided in the application. Methods for obtaining a sample of bone related tissue or cells from an individual; of assaying the concentration of infectious agents or factors produced by infectious agents or heat shock proteins produced in response to infectious agents; and of comparing the concentration of a marker from an individual to a control individual are well

known in the art. Therefore, it would not require undue experimentation to perform the method for detecting osteoporosis in an individual as defined by claims 1-19 of the present application.

(ii) The Examiner has not established a *prima facie* case of obviousness because the Examiner has not provided a reasonable expectation of success and has not provided the motivation to combine the cited references. While the Examiner argues that Findlay and Nair or Findlay and Reddi disclose each and every element of the claims of the present application, it is clear from the discussion above that they do not. Findlay discloses a method of measuring **internal** regulators of bone remodeling. Nair discloses that mammalian and bacterial molecular chaperones can stimulate bone resorption; not be predictive of osteoporosis. Reddi discloses that bacterial molecular chaperones can stimulate bone resorption. Findlay, Reddi, and Nair alone or in combination do not lead one of ordinary skill in the art to a method of detecting osteoporosis in an individual that contains the steps of measuring an infectious agent such as bacteria, or a factor produced by an infectious agent, or endogenous factors that are altered in expression due to infection, as defined by the claims of the present application, with a reasonable expectation of success.

For the foregoing reasons, Appellant submits that claims 1-19 are patentable.

Respectfully submitted,



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Claims Appendix: Claims On Appeal

1. A method of detecting osteoporosis in a individual to be tested comprising:

a) obtaining a sample of a bone related tissue or cells; and

b) assaying the concentration of at least one marker selected from the group consisting of infectious agents, a factor produced by an infectious agent, and heat shock proteins (HSPs) produced in response to an infectious agent, and

c) comparing the concentration of the at least one marker with the concentration of the marker in a sample of the same bone related tissue or cells from a control individual who does not have osteoporosis.

2. The method of claim 1 further comprising comparing the concentration of a first marker with concentrations of same marker obtained from the same individual over a period of time.

3. The method of claim 1 wherein the marker is a HSP and the bone related tissue or cells are obtained under conditions that do not induce a change in the amount of one or more HSPs in the tissue or cells.

4. The method of claim 3 wherein the HSP is selected from the group consisting of HSP 70, HSP 60, HSP 90, gp 96, cpn10, cpn20, ubiquitin, and cpn 30.

5. The method of claim 2 wherein the time period between the first assay and the second assay is at least about 12 hours.

6. The method of claim 1 wherein the sample comprises bone cells or body fluid.

7. The method of claim 3 wherein the HSP is HSP 60.

8. The method of claim 3 wherein the HSP is HSP 70.

9. The method of claim 3 wherein the HSP is ubiquitin.

10. The method of claim 3 wherein the concentration of HSP is measured using an immunoassay.

11. The method of claim 3 wherein the concentration of HSP is measured using an assay for a nucleotide molecule encoding HSP.

12. The method of claim 1 wherein the infectious agent is selected from the group consisting of bacteria, viruses, protozoa, parasites and fungi.

13. The method of claim 1 wherein the infectious agent is selected from the group consisting of bacterial produced factors, viral produced factors, protozoal produced factors, parasitic produced factors and fungal produced factors.

14. The method of claim 12 wherein the bacteria is selected from the group consisting of *Staphylococcus aureus*, *Porphyromonas gingivallis*, *Eikenella corrodens*, *Actinobacilus actinomycetemcomitans*, *Prevotella intermedia*, *Campylobacter* rectus, *Staphylococcus epidermidis*, *Salmonella spp.*, *Escherichia coli*, *Neisseria gonorrhoea*, *Neisseria meningitis*, *Mycobacterial tuberculosis*, *Haemophius influenzae*, *Pasteurella multocida*, *B. bronchiseptica*, and *Fusobacterium nucleatum*.

15. The method of claim 1 wherein the infectious agent is a bacterially produced factor selected from the group consisting of endotoxin-LPS, gapstatin, and dermonecrotic toxin (DNT).

16. The method of claim 15 wherein the factor is selected from the group consisting of gapstatin and dermonecrotic toxin.

17. The method of claim 15 wherein the factor is gapstatin.

18. The method of claim 15 wherein the factor is dermonecrotic toxin.

19. The method of claim 14 wherein the bacteria is selected from the group consisting of *Staphylococus aureus*, *Actinobacillus actinomycetemcomitans* , *Bordetella bronchiseptica*, and *Fusobacerium nucleatum*.

Evidence Appendix

None.

Related Proceedings Appendix

None.

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